Remarks

Status of the Claims

Claim 9 has been cancelled. Claims 10-13, 17, 18, 20, and 22-35 have been amended. Support for the amendments can be found, e.g., page 12, lines 5-21 and the originally filed claims. No new matter has been added.

Rejection Under 35 U.S.C. § 112, First Paragraph

Reconsideration is respectfully requested of the rejection of claims 9, 10, 11, and 18 under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement. Specifically, the Office alleged that the instant specification does not provide written description for a composition comprising a COX-2 inhibitor, 5-LO inhibitor and an immunosuppressive drug.

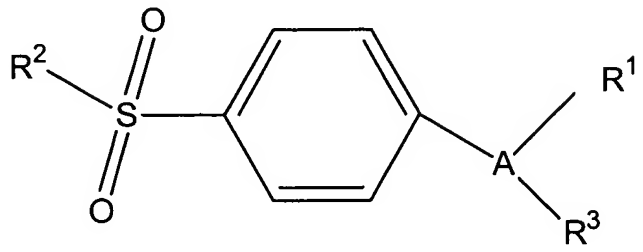
Applicants believe that the present amendments overcome the written description rejection for the reasons set forth below and the arguments detailed in Amendment E, dated May 24, 2004.

In view of the cancellation of claim 9, the written description rejection of this claim is moot.

With respect to the pending claims, Applicants have amended the terms "cyclooxygenase-2 inhibitor" and "5-lipoxygenase inhibitor" to "cyclooxygenase-2 **selective** inhibitor" and "5-lipoxygenase **selective** inhibitor," respectively. Support for these amendments can be found, e.g., on page 12, lines 5-21.

In addition, cyclooxygenase-2 selective inhibitors are claimed structurally, and are selected from 5-bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-thiophene, N-[2-cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide, 1,1-dioxide-4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide, and

compounds of Formula I or pharmaceutically acceptable salts of compounds having Formula I



wherein each of the substituents are defined. Support for this amendment can be found in the originally filed claims and in specification, e.g., on pages 9-10.

With respect to "5-lipoxygenase selective inhibitors," they are defined in the specification as "compounds which selectively inhibit 5-lipooxygenase with an IC_{50} of less than about 10 μM. More preferably, the 5-lipoxygenase inhibitors have an IC_{50} of less than about 1 μM." (Emphasis added.) See page 12, lines 17-21 of the specification. In addition, the specification discloses well over 150 examples of available compounds exhibiting selective 5-LO inhibition (see pages 13-14 of the specification).

The specification discloses a number of classes of immunosuppressants that may be employed in the composition of claim 10 along with examples of specific compounds belonging to each class. In particular, the specification states the immunosuppressant may be an antiproliferative agent, antiinflammatory-acting compound or an inhibitor of leukocyte activation selected from the following compounds:

> ...a cyclosporin compound, or Fujisawa FK-506 (macrolide lactone) compound, or rapamycin, or a glucocorticoid, or an antiproliferative agent, or a monoclonal antibody such as an anti-CD3 (anti-T cell receptor antibody) or anti-CD5/7 or anti-CD4 agent, or an anti-IL-2 receptor (anti-cytokine receptor type antibody) agent, or an anti-IL-2 (anti-cytokine antibody), or Nippon NKT-01 (15-deoxyspergualin) or Syntex RS-61443.

See pages 11-12 of the specification.

Furthermore, Applicants turn the Examiner's attention to dependent claims 11-19 and 22-38, which detail identities of COX-2 selective inhibitors, 5-lipoxygenase selective inhibitors and immunosuppressive drugs. Moreover, each of claims 10-20 and 23-38 require COX-2 selective inhibitors, 5-LO selective inhibitors, or immunosuppressants having a recited chemistry such that a skilled artisan could make or use the composition in each of these claims without undue experimentation.

Accordingly, Applicants submit that based upon the recited function of each component of the claim 10 composition and the number of structures provided in the specification for each component, a skilled artisan would discern that the applicants were in possession of the invention.

Rejection Under 35 U.S.C. § 112, First Paragraph

Reconsideration is respectfully requested of the rejection of claims 9, 10, 11, and 18 for failing to comply with the enablement requirement. Applicants respectfully disagree.

Applicants believe that the present amendments overcome the enablement rejection. With respect to *Wands* factors, they were addressed in detail in Amendment E.

Claim 9 has been cancelled, rendering the enablement rejection moot.

Claim 10 is directed toward a composition comprising a **5-lipoxygenase selective inhibitor**, an **immunosuppressive drug** selected from antiproliferative agents, antiinflammatory-acting compounds and inhibitors of leukocyte activation, and a **cyclooxygenase-2 selective inhibitor** selected from 5-bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-thiophene, N-[2-cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide, 1,1-dioxide-4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-

5-yl]-methanesulfonamide, and compounds of Formula I or a pharmaceutically acceptable salt of a compound having Formula I. Claims 11-19 depend from claim 10.

Claim 20 was amended to replace the trademark names of Dupont Dup 697, Taisho NS-398, meloxicam and flosulide with their chemical names, as detailed in Amendment B, dated October 16, 2002. It is narrower in scope than claim 10, and is directed towards a pharmaceutical composition comprising a therapeutically-effective amount of a 5-lipoxygenase selective inhibitor, a cyclosporin compound and a cyclooxygenase-2 selective inhibitor selected from 5-bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-thiophene, N-[2-cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide, 1,1-dioxide-4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide and compounds of Formula I or a pharmaceutically acceptable salt of a compound having Formula I. Cyclosporin compound belongs to the group of immunosuppressive drugs.

Claim 22 is directed to a composition comprising a 5-lipooxygenase selective inhibitor selected from a limited number of named compounds, a cyclooxygenase-2 selective inhibitor selected from a limited number of named compounds, and a cyclosporin compound. Claims 23-35 depend from claim 22.

Claim 36-38 are independent claims directed to compositions comprising a single cyclooxygenase-2 inhibitor, a single 5-lipooxygenase selective inhibitor, and a cyclosporin compound.

The specification provides detailed guidance that fully enables a skilled artisan to prepare a cyclooxygenase-2 selective inhibitor employed in the combination of claim 10. More specifically, any one of reaction schemes I-X may be utilized to prepare a cyclooxygenase-2 selective inhibitor having formula I (see pages 27-40 of the specification). The specification further discloses 3 examples of compounds that were made following the steps of one of the reaction schemes. See pages 41-43 of the specification. In addition, the specification discloses well over 150 examples of

available compounds exhibiting selective 5-LO inhibition (see pages 13-14 of the specification). The specification also discloses a number of classes of immunosuppressants that may be employed in the composition of claim 10 along with examples of specific compounds belonging to each class (see the discussion under the written description section).

The specification also details biological testing of an embodiment of the composition of claim 10 (and also claims 20 and 22) in a "transplantation and evaluation of graft rejection" model. See pages 43-45 of the specification.

Thus, a skilled artisan is fully empowered to make and use the combination of claim 10 without undue experimentation. Regarding claims 20 and 22, the combination of compounds described therein represents a subset of compounds of claim 10. Claim 20 requires a pharmaceutical formulation of a 5-lipoxygenase selective inhibitor, a cyclosporin compound and a cyclooxygenase-2 selective inhibitor selected from 5-bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-thiophene, N-[2-cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide, 1,1-dioxide-4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide and compounds of Formula I or a pharmaceutically acceptable salt of a compound having Formula I. Applicants note that preparation and use of pharmaceutical compositions are described in detail on pages 45-49. The use of compounds of claim 20 is enabled for the same reason as the use of compounds of claim 10. Hence, claims 20 and 22 are enabled. In view of the fact that claims 36-38 relate to compositions comprising a single cyclooxygenase-2 inhibitor, a single 5-lipooxygenase selective inhibitor and a cyclosporin compound, Applicants also submit that these claims are enabled.

Rejection Under 35 U.S.C. 102(b)

Reconsideration is respectfully requested of the rejection of claim 9 as being anticipated by Fung-Leung (CA: 123:306186). Fung-Leung describes the use of

tepoxalin, a dual 5-lipooxygenase and cyclooxygenase inhibitor in combination with cyclosporin.

In view of the present amendments, Applicants submit that this rejection of claim 9 is moot and respectfully request its withdrawal. Claim 10 is novel over Fung-Leung as it requires a composition comprising a 5-lipooxygenase selective inhibitor, an immunosuppressive drug selected from antiproliferative agents, antiinflammatory-acting compounds and inhibitors of leukocyte activation, and a cyclooxygenase-2 selective inhibitor selected from 5-bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-thiophene, N-[2-cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide, 1,1-dioxide-4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide and compounds of Formula I or a pharmaceutically acceptable salt of a compound having Formula I.

Conclusion

In light of the foregoing, Applicants request withdrawal of claim rejections and solicit an allowance of the claims.

Applicants request an extension of time to and including January 25, 2005 for filing a response to the above-mentioned Office action. A check in payment of the applicable extension fee is enclosed.

The Commissioner is hereby authorized to charge any deficiency or overpayment of the required fee to Deposit Account No. 19-1345.

Respectfully submitted,

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